EXHIBIT A

European Patent No. 764 447

(Application No. 96114439.1)

Bayer Corporation

Opposition by Baxter Healthcare Corporation

Statement of opposition

1 October 2004

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1 October 2004

Eric Potter Clarkson
For Opponent Baxter
Healthcare Corporation

Contents

1. REQUESTS AND GROUNDS OF OPPOSITION

The patent is opposed in its entirety under Article 100(a) and Article 100(c) EPC.

As a main request, we request revocation of the patent.

As an auxiliary request, we request oral proceedings if the Opposition Division would otherwise refuse our main request.

2. LACK OF INVENTIVE STEP

The patent is opposed under Article 100(a) EPC, due to a lack of inventive step according to Article 56 EPC.

2.1 Lack of Inventive Step of Claim 1 over D1 and D2

D1 (Neurath US 4 540 573) and **D2** (Tenold US 4 396 608) were discussed extensively during the examination of the application leading to the opposed patent. However, with respect, the Examining Division were wrong to grant a patent in the light of D1 and D2.

Our basic position, which is the same as the examiner's initial position, is that the claimed subject matter was obvious over a combination of D2 and D1. In formal terms, D2 can be taken as **the closest item of prior art**. It discloses a process for obtaining an immune serum globulin preparation having low anti-complement activity (ACA). It does not disclose a process that is said to reduce viral titre. A person skilled in the art, wishing to have a product that is as safe as possible, will therefore wish to combine it with a process that reduces viral titre. The **problem** can thus be regarded as the reduction of viral titre in the D2 product. D2 indicates (column 5, lines 26 to 29) that the D2 process can be applied to essentially any gammaglobulin composition that is the same as Cohn Fraction II or Cohn Fraction III filtrate. At column 1, lines 8 to 12, D1 indicates that its virus production process can be applied to any blood fraction. The use of Cohn Fraction II and Cohn Fraction III, and immune serum globulin, is specifically disclosed at column 6, lines 59 to 61. It was therefore obvious to use the D1 process to reduce viral titre in the context of the D2 immunoglobulin preparations and thereby provide the **solution** to the problem.

Although it is not necessary to combine **D3** (Yang *et al*, 1994) with D1 and D2 to arrive at the claimed subject matter, **D3** is evidence that those in this art had already used the solvent-detergent (SD) method of D1 to reduce viral titre in certain immunoglobulin preparations, and there was no reason to suppose that they would not have used it for the D2 preparations.

The applicants put forth various arguments in order to have the application allowed, even in the light of D1 and D2. We shall now address each of these and

show that the argument was not soundly based on scientific facts, or was irrelevant.

2.1.1 The apparently increased ACA of the SD product was an artefact

It was an important part of the applicants' submissions, and appears to have led to the granting of the opposed patent, that the allegedly increased ACA of the product of the SD step cannot be attributed to the production of aggregates. See, for example, Tables 3 and 4 in the patent, where there was apparently a high ACA prior to the incubation step even though the level of aggregates was quite low. The applicants seem to have taken the position that, if the person skilled in the art had combined D1 and D2, he would have found that the ACA was increased; he would have tested for aggregates and he would have found that they were not significantly present; and, having previously taken the view that the only point of the D2 process was to reduce the level of aggregates, he would have concluded that the D2 process was going to be ineffective in reducing ACA. The gap in the applicants' logic should be immediately apparent to the Opposition Division. The scenario that is being imagined is one in which D1 and D2 have *already* been combined and so the person skilled in the art would already have arrived at Claim 1. Hence, presumably, he would have created a product with a low ACA.

However, perhaps more importantly, it is actually not true that the SD step results in a product with a raised ACA. We enclose as **D4** an experimental report in which a Cohn Fraction II-derived composition was subjected to SD treatment and the ACA of the product was compared to that of the product without SD treatment. The following results were obtained:

		With SD treatment	Without SD treatment
Protein yield in the final bulk (g/l plasma)		5.14	5.17
Protein concentration in the final bulk (g/l)		101.2	100.1
Molecular size distribution	% aggregates	0.1	0.1
	% oligo/dimers	2.0	2.1
	% monomers	98.0	97.8
Cellulose acetate electrophoresis (% γ-globulin)		99.7	99.8
ACA titre (CH_{50}U/50mg protein)		45.6	45.6

Hence, whether the person skilled in the art tested the effect on the ACA level of the SD step (i) at all, or (ii) before deciding to combine D1 with D2, or (iii) after combining D1 and D2 (in order to see whether the combination had been successful) is completely irrelevant since the SD step does not raise ACA.

Note also the finding in D3 that

> "Complement binding was low in the native IGIV preparations"
>
> (D3, page 343, five lines above "Conclusions").

In D3, a comparison was made between Venoglobulin-I and Venoglobulin-S, the latter having been subjected to the SD process of D1. Both of these are "native" IGIV preparations, as opposed to the heat-aggregated preparations that were also made. See Figs 1 to 3. The low complement binding of the SD-treated product shows that, contrary to the applicant's assertions, the SD treatment does *not* raise ACA.

The patentee's elevated ACA may have been due to the extreme conditions to which the IG was subjected during the SD incubation. See for instance page 5 at [0025], which describes the incubation at pH7 at 30°C for ten hours. The non-SD treated IG was subjected to the same harsh conditions, and ACA was not elevated thereby; however, this only demonstrates that the patentee's particular choice of SD treatment plus their choice of incubation conditions caused the elevated ACA titre. As demonstrated by our data above, one with experience of and knowledge about IgG protein would have chosen a solvent and detergent from D1 and processed the protein under conditions that would not raise ACA titre.

The whole basis on which the patent was apparently granted can therefore be seen to be insecure in that there was no reason why the person skilled in the art, starting from D2, would not have added to it the D2 process and, having done so, arrived at a successful result.

The examiner was perfectly correct in his first communication to indicate that the claimed subject matter represents simply an uninventive combination of D2 and D1.

2.1.2 D2 did not teach away from a combination with D1

In the initial communication from the Examining Division, dated 6 December 2000, the examiner correctly took the position that the D2 process, which was intended to reduce anticomplement activity (ACA), could be applied to any suitable gammaglobulin preparation. See, for example, D2 column 5 lines 26 to 29:

> *"Gamma globulin obtained by any process which has essentially the same composition of protein components as found in the Cohn Fraction II or Fraction III filtrate can be used as starting material in the present process."*

The D2 process was not intended to reduce viral contamination of the product. Hence, as noted above, in order to reduce viral contamination, some other step would need to be employed. D1 taught the so-called "solvent-detergent" process, which became increasingly popular and accepted in the years between the publication of D1 (1985) and the priority date of the opposed patent.

On page 3 of their letter dated 6 April 2001, the applicants suggested that a person skilled in the art would have been dissuaded from combining the D2 process with the D1 process since, at column 4, lines 42 to 47, D2 refers to an advantage of the D2 invention being that it is free of chemical modification. The impression that the applicants tried to give was that the SD method of D1 would have been regarded as amounting to, or leading to, "chemical modification such as occurs in reduction-alkylation, β-propiolactone treatment, and the like". However, if one looks properly at the passages of D1 that were cited by the applicants, namely column 1 lines 60 to 63 and column 2 lines 38 to 45, it can be seen that the D1 process was being presented as an advantageous *alternative* to these prior art processes. Whereas the prior art processes resulted in denaturation of the desired protein or carcinogenic residues remaining in the product, the invention of D1 avoided this.

The D1 process does not result in chemical modification of the desired protein. Hence, the passage in D2 that was referred to by the applicants would not have dissuaded a person skilled in the art from combining the D1 and D2 references.

2.1.3 D2 would not have directed attention away from an increase in ACA during a viral inactivation process

On page 4 of their letter of 6 April 2001, the applicants advance another argument, namely that, because D2 teaches that ACA activity is increased as a result of denaturation during the fractionation procedure, the reader's attention would have been drawn away from exploring an increase in ACA due to a viral inactivation process. In fact, D2 itself says nothing about any viral inactivation process. There is no evidence that the reader of D2, who might have been contemplating combining the D2 process with the D1 process, would have assumed anything about whether the D1 process increased ACA.

2.1.4 An incubation of the type claimed was inherent in D2

Finally, in the letter of 6 April 2001 (first complete paragraph of the last page), the applicants suggested that, even if D1 and D2 had been combined, there would have been no suggestion to use an incubation to control increased ACA arising from a viral inactivation step. In fact, an incubation of precisely the type now claimed was inherent in the D2 process.

Referring to column 9, line 12, the material obtained at that point of the process had an ionic strength of 0.001 and a pH of 4.2. In the final step of opposed Claim 1, the ionic strength is said to be less than 0.001. However, as can be derived from appeal board decision T0594/01 (Shell/alkylene glycols), this wording does not distinguish the claim from a prior art disclosure of 0.001. The

pH in the claim is said to be between 3.5 and 5.0, which clearly includes 4.2. The step of making the material tonic at lines 13 to 15 would not have altered the ionic strength or the pH, since the material that was added was maltose. At lines 19 to 20, it can be seen that the product was stored at room temperature for at least six months. This therefore complies with the requirements in the claim for the solution to be incubated at 2 to 50°C for at least 10 days.

Hence, D2 discloses an incubation of the kind defined in part (c) of opposed Claim 1, and this incubation would inherently have reduced the ACA activity, if (contrary to our belief) this had been raised by the SD step of the process.

2.1.5 D2 was not restricted to prevention of aggregates

Towards the end of page 4 of their letter of 22 January 2002, the applicants suggested that D2 teaches reducing anticomplement activity solely by reducing aggregation. In fact, one should note the following passage in D2, at column 4, lines 48 to 51:

> *" An important feature of the product of the invention is that it is substantially free of actual and latent anticomplement activity and <u>also</u> substantially free of polymeric material or "aggregates"."* (our emphasis)

In any case, the reader would not be particularly concerned with the manner in which the ACA was reduced but would instead have been led to have used the D2 process whenever there was risk of anticomplement activity.

2.2 Lack of inventive step of subsidiary claims

Claims 2 to 6 further define the resulting antibody solution as having less than certain threshold amounts of ACA, in the context of differing concentrations of antibody. No further process steps are specified and it must be assumed that the basic process inevitably results in these low levels of ACA. Hence, having made the obvious combination of D1 and D2, the person skilled in the art would apparently inevitably arrive at antibody solutions falling within Claims 2 to 6.

Similarly, it would appear that the product resulting from a combination of D1 and D2 will inevitably fall within **Claim 7**. In addition, we note that the SD-treated immunoglobulin preparations of D3 had high levels of monomer, amounting to about 90%. See Table 6. It should be noted from that table that the SD treatment seems to have no significant effect on the level of monomer. Hence, it seems that the monomer level is governed by the monomer level in the starting material for the SD process. In other words, the high monomer level that was apparently obtained in the context of the patent can be attributed to the use of the D2 process, not to any contribution provided by the patent itself.

In **Claims 8 to 10**, the tonicity of the antibody solution that results from step (b) is adjusted to a physiological value, without altering the ionic strength, for example by adding a carbohydrate such as maltose. This is disclosed in D2 at column 9,

lines 12 to 15, and would inevitably be done as a result of a simple combination of D1 and D2. In **Claims 11 and 12**, the tonicity is specified but the values indicated do not add anything significant to Claim 8, since the values encompass normal physiological values. The osmolarity of blood is abut 280 to 300 mosm/kg. A 10% maltose solution (D2, Col. 9, line 14) has an osmolarity of about 294. . In **Claims 13 and 14**, the tonicity is adjusted by adding an amino acid, such as glycine. This was disclosed in D2, at column 7, line 5, as an alternative to using a carbohydrate such as maltose.

In **Claim 15**, the trialkylphosphate is TNBP and the detergent is either polysorbate 80 or sodium cholate. The use of the TNBP and polysorbate 80, in the specific context of applying the SD process to an immunoglobulin preparations, was disclosed in D3 at page 338, left-hand column, penultimate paragraph. If the patentees were to limit the claim to the use of cholate, we note that sodium deoxycholate (which is equivalent to the sodium cholate used in the patent) was disclosed in D1, at column 8, lines 5 to 6.

Finally, in **Claim 16**, the antibody solution is said to be subjected to the SD treatment at a pH between 3.5 and 6.0. D2 had shown, at column 8, lines 47 to 48, that a relatively low pH was desirable in the context of an immunoglobulin preparation. There seems to have been no reason for the person skilled in the art to have ignored this when combining D2 with D1.

Hence, it can be seen that all of the features of the subsidiary claims can be derived from D1 and D2 themselves, with D3 providing additional evidence that the particular combination of solvent and detergent specified in Claim 15 was one that had already been used in the art in the specific context of immunoglobulin preparations.

Claim 1 of the patent represents a simple combination of D1 and D2, and the subsidiary claims do not add anything inventive.

3. ADDITION OF SUBJECT MATTER

The patent is also opposed under Article 100(c) EPC, because subject matter has been added to the specification of the application was filed.

Claim 1 states that step (a) is conducted until the titre of the viruses is reduced by at least $4\log_{10}$, whereas the claim as filed made no reference to this parameter. Referring to the typed manuscript of the specification as filed, page 3, just above the heading "brief description of the figure", refers to a substantial reduction (ie at least 4 logs) in the titre of lipid enveloped viruses. However, this is said to be the result of the viral inactivation step *in a model system*. The model system in question is set out on pages 6 and 7. It is stated at the end of paragraph 1 on page 7 that a greater than 5.2 $\log_{10}$ reduction in the level of one specific virus (HIV) was obtained and a greater than 4.0 $\log_{10}$ reduction in the level of another specific virus (BVDV) was obtained. However, neither of these is presented as providing an experimental endpoint to aim for when conducting the viral inactivation step.

Rather, the two values are simply presented as the results of the particular process conditions set out on pages 6 and 7. In addition, in the context of a threshold of 4.0 $\log_{10}$ viral reduction, the passage on page 7 was specific for the BVD virus, whereas Claim 1 is silent concerning the particular virus the levels of which are being reduced. Indeed, the fact that the same process resulted in a greater reduction of the level of HIV demonstrates that the log reduction figures are specific to each virus and cannot be generalised to viruses as a whole.

Hence, although we acknowledge that there is a disclosure of the 4.0 $\log_{10}$ threshold in the description as filed, this has been generalised away from the specific experimental parameters of the model system set out on pages 6 and 7 and it has been generalised away from the particular virus (BVDV) in the context of which it was disclosed on page 7.

The introduction of this threshold in Claim 1 appears to have been introduced at the instigation of the examiner; see the communication of 5 July 2002. However, of course, this does not make it any more allowable in an objective sense. The examiner referred to D1 in this context. It is true, firstly, that D1 states that its process can be used in order to obtain a 4 log inactivation of virus (see, 4, lines 57 to 62) and that the application leading to the opposed patent refers (at page 2, line 3) to the D1 reference. However, the cross-reference in the opposed patent to D1 is not presented in the context of providing a definition of when viral inactivation has been achieved.

Hence, the amendment to Claim 1 results in the presentation of new information to the reader, beyond what was disclosed in the application as filed (even taking the cross-reference to D1 into account), namely the fact that a particular viral reduction threshold of $4\log_{10}$ should be used in order to devise a viral reduction step in accordance with the invention.

4. DOCUMENTS SUBMITTED

D1 US 4 540 573 (Neurath *et al*)

D2 US 4 396 608 (Tenold)

D3 Yang *et al* (1994) *Vox Sang.* **67**, 337-344

D4 Experimental Report

1 October 2004

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5. CONCLUSION

We are conscious that this opposition is based primarily on the same two prior art documents that were considered by the Examining Division. However, the new technical information that we have submitted should convince the Opposition Division that D1 and D2 would have been combined by the person skilled in the art in order to provide a low ACA, low viral titre ISG product. The patent should therefore be revoked.

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D4

Investigation of the effect of solvent detergent (SD) treatment on immunoglobulin-containing preparations

Study Design

A 25% cold alcohol precipitation was carried out with a redissolved, clarified Cohn Fraction II+III precipitate suspension to recover an IgG-enriched paste containing more than 86% of gammaglobulin. The IgG intermediate was resuspended in water for injection (WFI) and clarified. The filtrate of this dissolved paste was then either directly applied to a CM Sepharose column without SD treatment or treated with a SD mixture containing TNBP, Triton X-100 and Tween 80 at approximately pH 5.2, 20-25^{0}C for 60 minutes. The final concentrations of the SD components were 0.3% (v/v) TNBP, 1.0% (v/v) Triton X-100 and 0.3% (v/v) Tween 80.

At the end of SD treatment, the protein solution was loaded to a CM-Sepharose column to bind the immune globulin. SD components were removed by washing with a 10 mM sodium acetate buffer pH 5.5. Immune globulin, from both with and without SD treatment, was subsequently eluted from the CM column and the eluate was diluted and loaded onto an anion exchange column to facilitate binding and removal of IgA. For both runs the same sets of columns were used.

The fall through from the anion exchange column containing the immune globulin was concentrated and the buffer exchanged by dialfitration against a buffer containing 0.25 M glycine, pH 4.2.

The processed IgG preparations were then tested for protein concentration, IgG and IgA content, molecular size distribution (MSD), purity and anti-complement activity (ACA).

Results

The following table summarises the study results:

		With SD treatment	Without SD treatment
Protein yield in the final bulk (g/l plasma)		5.14	5.17
Protein concentration in the final bulk (g/l)		101.2	100.1
Molecular size distribution	% aggregates	0.1	0.1
	% oligo/dimers	2.0	2.1
	% monomers	98.0	97.8
Cellulose acetate electrophoresis (% γ-globulin)		99.7	99.8
ACA titre (CH_{50} /50 mg protein)		45.6	45.6